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TITLE: Therapeutic uses of emu oil

DATE-ISSUED: December 5, 1995

INVENTOR-INFORMATION:

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PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
9208470	May 1992	WO	

OTHER PUBLICATIONS

"Emu Oil: This Composition Has No Competition"--Emu Today & Tommorrow--Nov. 1994 pp. 16-18 & 20, 22.
"An Analysis Of Emu Oil: Cutting The Fat!"--Emu Today & Tommorrow--Nov. 1994, pp. 131, 133, 135, 138, 139.

ART-UNIT: 152

PRIMARY-EXAMINER: Venkat; Jyothsna

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ABSTRACT:

Emu oil is therapeutically used in methods for lowering cholesterol, triglycerides and low density lipoproteins and increasing high density lipoproteins; preventing and treating allergies; preventing scarring; treating headaches; preventing nose bleeds; treating and preventing cold and flu symptoms; and relieving discomfort associated with menstruation. Additionally, emu oil acts as an effective chemical buffer in combination with glycolic acid.

2 Claims, 0 Drawing figures
Exemplary Claim Number: 1

BRIEF SUMMARY:

1 BACKGROUND OF THE INVENTION

2 The present invention relates to uses of emu oil for preventing and treating a variety of ailments.

3 Emu oil has been used in Australia as an Aboriginal liniment, the oil being rendered from the bird's fat. The oil is used in cosmetics and cosmetic-related items, including wrinkle-retarding emollients, cosmetic bases and moisturizers for the face and body. It was traditionally used by the Aborigines for treating burns and as a remedy for arthritis and sports injuries. In Australian pharmacies, emu oil is sold as a liniment and a lubricant. Additionally, emu oil is used as a massage oil.

4 According to one publication, emu oil alone has been unable to reduce inflammation, even though the Aboriginal tribes of Australia have been using emu oil for arthritis. Instead, PCT/AU91/00517, International Publication No. WO 92/08470 found it necessary to add a miscible diluent, such as isopropyl alcohol, amyl alcohol or acetate, ethyl, methyl or isopropylsalicylate, t-tree oil, eucalyptus oil, cineole, or the like, to emu oil to achieve an anti-inflammatory effect.

5 An important use of emu oil provided by the present invention is for lowering cholesterol for treating high cholesterol conditions. The primary constituents of emu oil are fatty acids. Others have utilized fatty acids for lowering cholesterol and/or for treating high cholesterol conditions.

6 U.S. Pat. No. 3,849,554 to Winitz uses a defined diet to reduce blood serum cholesterol. The diet includes amino acids, vitamins, minerals, essential fatty acids, including linoleic, linolenic and arachidonic, and carbohydrates, including glucose, maltose, and polysaccharides of glucose. Winitz finds its diet works to reduce blood serum cholesterol principally by controlling the type of carbohydrate in the diet. For example, Winitz finds an increase in cholesterol where sucrose is used.

7 DiTullio, U.S. Pat. 3,969,508, refers to lowering the concentration of plasma triglycerides using a hypolipidemic composition to produce hypolipidemic activity in hyperlipidemic subjects. The active ingredient used is 4-(2-thenoyl)-2,3-dichlorophenoxy acetic acid. DeTullio finds, as a result of its method, that plasma cholesterol concentrations are not significantly effected and there is no significant effect on free fatty acids.

8 U.S. Pat. No. 4,472,432 to Iwamura refers to using alpha and beta unsaturated fatty acids from clams to improve lipid metabolism. Specifically, it provides a prophylaxis and remedy of hyperlipidemia and lipotropic effect and prophylaxis of hyterosclerosis arteriosclerosis. Iwamura refers to using 2-octadecenoic acid to decrease total cholesterol, triglyceride and blood serum and total lipid amount in addition to decreasing cholesterol and triglyceride in the liver.

9 Revici, U.S. Pat. No. 4,513,008 refers to a method of inactivating an enveloped

virus, such as herpes, using at least a C.sub.20-24 linear polyunsaturated acid.

10 U.S. Pat. No. 4,603,142 to Burger refers to using d-.alpha.-tocotrienol in a method for lowering cholesterol. According to Burger, its key ingredient, d-.alpha.-tocotrienol, is found in high-protein barley flour and lemon grass oil. Additionally, according to Burger, d-.alpha.-tocotrienol inhibits cholesterol biosynthesis.

11 Ward, U.S. Pat. No. 4,678,808, refers to intravenous emulsions of omega-3 fatty acid esters for supplying essential fatty acids. The omega-3-fatty acid ester of Ward is derived from marine oil. Ward refers to using omega-3-fatty acid esters for treating thrombotic diseases.

12 U.S. Pat. No. 4,851,437 to Revici refers to using tung oil for treating arteriosclerosis.

13 Beyer, U.S. Pat. Nos. 4,920,123 and 5,110,817, refer to a method for controlling and/or lowering serum triglyceride and/or serum cholesterol levels in mammals. In its method, Beyer uses pyrazinoylguanidines.

14 U.S. Pat. No. 4,999,380 to Berger refers to a process of treating lipoprotein disorders associated with cholesterol metabolism using a lipid from the black currant seed to increase high density lipoproteins (HDLs) and decrease low density lipoproteins (LDLs).

15 Wakabayashi, U.S. Pat. No. 5,034,414, refers to using fish oil fatty acids as an antithrombotic and an antiartherosclerotic.

16 U.S. Pat. No. 5,277,910 to Hidvegi refers to a process for preparing a pharmaceutical composition for selectively lowering the blood-lipid level. The composition includes saponins from alfalfa.

17 Mattson, U.S. Pat. No. 4,034,083 and Reissue No. 33,885, refer to compositions for inhibiting the absorption of cholesterol. The composition includes polyesters which act as fat substitutes and are not absorbable or digestible. According to Mattson, the polyesters interfere with the body's absorption of cholesterol. Accordingly, Mattson uses its compositions to treat hypercholesterolemia (high blood cholesterol). Mattson uses fatty acids to make its polyesters.

18 Jandacek, U.S. Pat. No. 4,005,195 and Reissue No. 33, 996, refer to compositions for treating hypercholesterolemia. The compositions referred to in Jandacek include liquid polyol fatty acid polyesters with anti-anal leakage agents. According to Jandacek, the polyesters interfere with the body's absorption of cholesterol. The anti-anal leakage agents are anti-laxative agents, such as a C.sub.12 or higher saturated fatty acid, for example, cocoa butter, palm oil, etc.

19 SUMMARY OF THE INVENTION

20 The present invention is directed to new uses for emu oil. It has been discovered that administration of emu oil on a regular basis results in lowering cholesterol, triglyceride and low density liproproteins (LDL's) and increasing levels of high density lipoproteins (HDL's). Additionally, regular use of emu oil results in improving the rate of growth and condition of nails, preventing and treating allergies, preventing nose bleeds, and preventing and treating headaches (especially migraine headaches). Additionally, emu oil can be used to prevent scarring when applied to a newly received cut or burn. It also diminishes old scars.

21 Stretch marks, such as those acquired during pregnancy, can be prevented by application of emu oil. Additionally, application of emu oil diminishes or completely erases existing stretch marks.

22 Emu oil can be administered as necessary for treating cold and flu symptoms,

including sore throats and nasal congestion. In the same manner emu oil can be taken as a remedy for the ailments related to menstruation.

23 Finally, emu oil can be used as a chemical buffer.

24 It is an object of the present invention to provide methods for the above-described uses of emu oil.

25 If is a further object of the present invention to provide modes of administration of emu oil for obtaining the benefits described above.

26 The above and other objects, features and advantages of the present invention will be described herein by a detailed description thereof.

27 DETAILED DESCRIPTION OF THE INVENTION

28 Emu oil is obtained from a large, approximately five feet tall, flightless bird of Australia known as an emu, Dromideius novaehollandiae. Emus are farmed for their meat, which is low in cholesterol and fat. The oil rendered from the emu is actually a semi-solid fat (i.e., fat and oil mixture) at room temperature, but will herein be referred to as an oil.

29 The fat and oil mixture is stripped from the carcass of the emu and can be melted to further liquify the oil. Emu oil obtained in this manner is yellow and is olfactorially offensive. It is possible, through refining processes, to remove the yellow color from the oil and reduce its odor. PCT/AU91/00517 refers to removing the yellow color from emu oil by exposing it to sunlight, page 8, and by subjecting it to chemical oxidation by mixing it with benzoyl peroxide in an organic solvent, page 9.

30 In PCT/AU91/00517 it was found that the remarkable anti-inflammatory effects of the emu oil composition, when mixed with a miscible diluent, disappeared upon removal of the yellow components of the emu oil. Accordingly, PCT/AU91/00517 is directed to using specifically the yellow component of the emu oil along with a miscible diluent. However, the present inventors have found upon refining emu oil to remove the yellow color and reduce its odor, there is no difference in the constituents of the oil, besides its impurities being removed, and the refined oil can be used according to the present invention. Accordingly, for the uses of emu oil in accordance with the present invention either the raw yellow oil or a refined oil can be used.

31 One type of refined emu oil is manufactured under the trademark KALAYA OIL and can be obtained from New World Technology, Inc. P.O. Box 7580 Greenwich, Conn., 06836-7580. Material Safety Data Sheet Information on such a refined oil are as follows:

IDENTIFICATION	
Product Name	EMU OIL
UN Number	None Allocated
Dangerous Goods Class	None Allocated
Subsidiary Risk	None Allocated
Hazchem Code	None Allocated
Poisons Schedule	Not Scheduled

TABLE 1

PHYSICAL PROPERTIES

Description: At 20.degree. C. it is a semi-solid white mass, at 600.degree. C. a practically clear yellow, colored liquid. Very slight odor.

Boiling Point: >150.degree. C.

Vapor Pressure: Not available

Specific Gravity: 0.9458 g/mL

Flashpoint: >140.degree. C.

Solubility in Water: insoluble

Water Content: <0.1% w/w

Refractive Index: 1.4642

Acid Value: 0.45

Saponification Value: 187.09

Peroxide Value: 1.475

Iodine Value: 70.97

Ester Value: 186.64

TABLE 2

Constituents (Fatty Acids)	Mean Content (%)
C14:0 myristic	0.2
C16:0 palmitic	30.7
C16:1 palmitoleic	4.2
C18:0 stearic	10.7
C18:1 oleic	46.3
C18:1 elaidic	0.7
C18:2 linoleic	6.5
C18:3 (9, 12, 15) linolenic	0.1

HEALTH HAZARD INFORMATION

HEALTH EFFECTS

Emu Oil is an edible oil.

INGESTION Emu Oil is non-irritant.

EYES Emu Oil is non-irritant to mucous membranes.

SKIN Emu Oil at room temperature is non-

	irritant to most skin types.
INHALATION	Emu Oil at room temperature does not present an inhalation hazard.
INGESTION	Since Emu Oil is edible, ingestion should not cause problems.
INHALATION	Not considered as harmful.
PRECAUTIONS FOR USE	
EXPOSURE	Not considered hazardous.
LIMITS	There are no known Threshold Limited Values (TLV) for Emu Oil.
VENTILATION	Precautions are not usually required.
PERSONAL PROTECTION	Personal protection is not required.
FLAMMABILITY	Not considered combustible under 140.degree. C.
SAFE HANDLING INFORMATION	
STORAGE & TRANSPORT	Emu Oil is an edible oil and should not pose problems with transportation or storage. However, it should not be stored or transported with toxic chemicals, flammable gases, explosives, oxidizing agents and spontaneously combustible substances. Store in a cool area and keep containers closed to avoid contamination from impurities.
SPILLS AND DISPOSAL	Contain using sand or earth and use as an absorbent (sand, sawdust, vermiculite) where appropriate. Collect and seal in properly labelled containers for disposal. Wash area down with excess water. Waste material may be incinerated under controlled conditions where permitted. Refer to local Waste Management Authority Regulations for other approved methods.
FIRE/EXPLOSION HAZARD	Remove containers from path of fire. Heating can cause expansion and rupture of containers. Keep containers cool with water spray.
EXTINGUISHING MEDIA	Carbon dioxide, dry chemical powder, BCF or alcohol stable foam.

32 Analysis by Dr. R. B. Longmore, BSc, MSc, PhD (manchr) of the refined oil by gas chromatograph yielded the following information:

TABLE 3

FAME Analysis, relative fatty acid content

Identity	Name	Mean content (%)	std. dev
C14:0	myristic	0.7	0.0(3)
C16:0	palmitic	26.7	0.2
C16:1	palmitoleic	5.4	0.1(3)
C18:0	stearic	11.3	0.3
C18:1	oleic	46.1	0.8

C18:1	elaidic	1.7	one sample detection
C18:2	linoleic	8.4	0.2
C18:3	(9,12,15) linolenic	0.6	0.0(1)

Note:
actual results: sample 1: C18:1 = 46.7%, 0.0% elaidic.
sample 2: C18:1 = 45.6, 1.75% elaidic.
When elaidic not quantified it may be integrated in C18:1 oleic peak.

33 Further analysis, by ORON Laboratories Pty. Ltd. on Dec. 21, 1993, of physical properties of the refined Emu Oil yielded the following information:

TABLE 4

TEST	RESULT
Weight per mL @ 20.degree. C.	0.9216 g/mL
Refractive Index @ 20.degree. C.	1.460
Acid Value	0.40
Saponification Value	189.84
Iodine Value	65.83
Peroxide Value	2.83
Ester Value	189.44
Water Content	Nil Detected
P-Anisidine Value	2.75
Totox Value	8.41

34 An independent study on the composition of refined emu oil vs. chicken oil was conducted in August 1993 by Mr. Donald A. Swift. The results of his analysis are reproduced below:

STATEMENT OF ANALYSIS	
Date of Report	27 August 1993
Sample Description	Refined emu oil Colourless semisolid oil; odourless; melts to clear oil

TABLE 5

FAME Analysis, relative fatty acid content Identity			
	Name	Mean Content (%)	STD Dev
C14:0	Myristic	0.0	0.0
C16:0	Palmitic	22.0	0.12
C16:1	Palmitoleic	1.3	0.12
C18:0	Stearic	6.8	0.44

C18:1	Oleic	62.4	1.5
C18:1	Elaidic	0.44	0.88
C18:2	Linoleic	6.9	0.41
C18:3	(9,12,15) Linolenic	0.0	0.0

STATEMENT OF ANALYSIS

Date of Report 20 August 1993
Sample Description Chicken Oil
Straw-coloured semisolid oil; characteristic odour; melts to clear oil

TABLE 6

FAME Analysis, relative fatty acid content

Identity	Name	Mean Content (%)	STD Dev
C14:0	Myristic	0.8	0.0 (1)
C16:0	Palmitic	14.2	1.2
C16:1	Palmitoleic	3.3	0.38
C18:0	Stearic	3.6	0.52
C18:1	Oleic	66.6	1.9
C18:1	Elaidic	1.6	0.01
C18:2	Linoleic	9.3	0.28
C18:3	(9, 12, 15) Linolenic	0.9	0.

35 FATTY ACID ANALYSIS OF EMU SUBCUTANEOUS AND INTESTINAL FAT

36 SAMPLE PREPARATION

37 Samples of fat from the freezer were cut in sections, and slices cut through the sections to provide representative samples of the fat. The slices were placed in a beaker and microwaved at the lowest setting to melt the fat, with the fat temperature not exceeding 100.degree. C.

38 One drop of each sample of fat was then placed in a sample tube with 2 drops of T.A.M.H..sup.1 and 200 .mu.l of toluene. The tube was then shaken, rotated for one hour and then placed in the freezer to await G.C. analysis.

G.C. PARAMETERS

Column Type: HP Ultra
Carder Gas: H.sub.2 at 80 KPa
Column Length: 25 meters

Column Diameter: 0.2 mm
Initial Temperature:
195.degree. C. for 18 minutes, then
Temperature Rise of 15.degree. C./minute to the,
Final Temperature of 310.degree. C. for 1 minute

TABLE 7

Fatty Acid	Subcutaneous Fat (#185) 1	2	Mean	Intestinal Fat (#78) 3	4	Mean	Subcutaneous Fat(NT#5) 5	6	Mean
14:1	trace		trace			trace			trace
14:0	0.5	0.5	0.5	0.4		0.5	0.4	0.3	0.3
16:1	2.7	2.6	2.6	3.8		3.9	3.8	4.3	4.3
16:0	22.0		21.9	22.0	22.9	23.8	23.4	19.6	19.7
18:2	16.3		16.4	16.4	10.0	9.9	10.0	5.8	5.8
18:3	0.7	0.6	0.6	0.5		0.4	0.4	0.2	0.2
18:1 (9)	44.3		43.9	44.1	47.9	47.6	47.8	56.7	56.6
18:1 (7)	1.8	2.0	1.9	2.9		2.5	2.7	2.5	2.4

18:1 (trans)
0.3 0.4 0.4 0.4
0.3
0.4 0.2 0.1 0.2
18:0 10.4
10.5
10.4 10.2
10.0
10.1
10.0
10.0
10.0
20:1 0.4 0.4 0.4 0.04
0.4
0.4 0.4 0.4 0.4
Other 0.6 0.8 0.7 0.6
0.7
0.6 0 0.2 0.2

NOTE:
18:2 and 18:3 percentages were obtained from a small injection of sample (0.2 .mu.L) whilst all other results were from a large injection. Sample 1, 2, 3, 4 were of white appearance, solid at room temperature whilst samples 5, 6 were of yellow appearance and partially liquid at roo temperature.

39 Additionally, international application PCT/AU91/00517 includes a mass spectral analysis of emu oil and other products in its Table 5. This table is reproduced below as TABLE 8.

TABLE 8

GLC - Mass Spectral Analysis of Emu Oil and Other Products (as % of Total)
Identification no. (batch)
135
136
137
138
157
158*
159'
181
203 202

Palmitic (C16:0)
24.1
26.0
31.1
28.2
27.3
32.0
26.5
27.5
13.2
5.6
Palmitoleic (C16:1)
ND ND ND ND ND ND ND 4.0
<1.0
ND
Stearic (C18:0)
10.7

11.6
9.0
10.5
9.9
11.3
9.2
8.4
2.7 1.4

Oleic (C18:1)
59.9
58.1
55.2
56.6
43.7
39.8
44.2
54.2
62.4
59.9

Linoleic (C18:2)
5.3
4.3
4.7
4.7
7.4
6.8
8.1
5.9
20.1
23.8

a-Linolenic (C18:3)
ND ND ND ND 11.7
10.1
11.9
ND 1.7 9.1

g-Linolenic (C18:3)
ND ND ND ND ND ND ND ND ND ND

---

* Sediment after cooling EO 157 to 10.degree. C.
'Supernatant after cooling EO 157 to 10.degree. C.
202 Canola Brand polyunsaturated cooking oil
ND Not detectable
" A commercial preparation of EO diluted with peanut oil (4.1 v/v)

40 International Application PCT/AU91/00517 also includes a comparison of the fatty acid composition of free range chicken and emu fats in its Table 6. This table is reproduced below as TABLE 9:

TABLE 9

Comparison of Fatty Acid Composition of Free Range Chicken and Emu Fats (Data generated after methoxide hydrolysis and GLC expressed as %).

Fatty Acid	Number Carbons	Unsaturation	Emu	Chicken
Myristic	C14	0	0.32	1.25
Palmitic	C16	0	21.27	22.03
Palmitoleic	C16	1	5.57	6.85
Stearic	C18	0	7.81	5.94

Oleic	C18	1	54.52	48.37
Linoleic	C18	2	7.24	12.06
Linolenic	C18	3	0.41	0.86
Arachidic	C20	0	0.37	0.51
Arachidonic	C20	4	<0.2	<0.2
Total poly-unsaturated Fatty Acids present			7.65	12.92

41 The inventors have found emu oil can be ingested at least once a day for lowering cholesterol and increasing rate of nail growth and condition, e.g. , durability of nails. The precise amount of emu oil ingested depends upon several factors including the requirements of the patient and the age and weight of the patient. Though emu oil should be taken daily for obtaining these therapeutic effects, the exact amount of the dosage is not critical, for example, some patients may benefit most from administration of from between two and ten milliliters of the emu oil. Others may find between three and seven milliliters of emu oil beneficial. Still others may ingest between four and six milliliters of emu oil. A preferable dose for adults is one teaspoon of emu oil per day.

42 Information regarding the use of fatty acids and certain natural oils for lowering cholesterol and treating conditions related to cholesterol metabolism, including, but not limited to, dosages of fatty acids and fat emulsions and forms of administration, are known to those with skill in the art as illustrated by the United States Patents Incorporated herein by reference. The following United States patents are incorporated herein by reference: Winitz U.S. Pat. No. 3,849,554; DiTullio U.S. Pat. No. U.S. Pat. No. 3,969,508; Iwamura U.S. Pat. No. 4,472,432; Revici U.S. Pat No. 4,513,008; Burger U.S. Pat. No. 4,603,142; Ward U.S. Pat. No. 4,678,808; Revici U.S. Pat. No. 4,851,437, Beyer U.S. Pat. Nos. 4,920,123 and 5,110,817; Berger U.S. Pat. No. 4,999,380; Wakabayashi U.S. Pat. No. 5,034,414; Hidvegi U.S. Pat. No. 5,277,910; Mattson U.S. Pat. No. 4,034,083, U.S. Pat. No. Re. 33,885 and Jandacek U.S. Pat. No. 4,005,195, U.S. Pat. No. Re. 33,996, regarding the information referred to in the preceding sentence and the subject matter encompassed by these patents.

43 Examples 1 and 2 illustrates the cholesterol lowering effects of daily ingestion of emu oil. As can be seen from Examples 1 and 2, emu oil is effective for lowering blood serum cholesterol. The patients in both Examples 1 and 2 have found the effectiveness of emu oil is greatest when it is taken on a regular basis and that the effectiveness of the emu oil for lowering cholesterol diminishes when emu oil is not taken on a regular basis.

DETAILED DESCRIPTION:

1 EXAMPLE 1

2 Mature human female aged 38 years ingests approximately 5 drops or one teaspoon of emu oil per day. Prior to this patient's ingestion of emu oil, testing on Jan. 6, 1993 yielded the following results:

Total cholesterol	272 mg/dl
LDL	193 mg/dl
HDL	58 mg/dl
Triglycerides	103 mg/dl

3 Subsequent to ingestion of emu oil, testing yielded the following results: Testing on Feb. 19, 1994, when patient was taking approximately one teaspoon of emu oil per day, but not on a regular basis:

Total cholesterol	231 mg/dl
HDL	43 mg/dl
Chol./HDL	5 mg/dl
LDL	171 mg/dl
Triglycerides	87 mg/dl

4 Testing on May 26, 1994, when patient was taking approximately one teaspoon of emu oil per day on a more regular basis:

Total cholesterol	210 mg/dl
LDL	132 mg/dl
HDL	66 mg/dl
Triglycerides	58 mg/dl

5 EXAMPLE 2

6 Mature human female aged 60 years ingests 7 to 10 drops of emu oil per day, approximately one teaspoonful. Patient has previously taken Mevocore for lowering her cholesterol and has suffered side effects, including hair loss. Patient does not suffer from side effects from ingesting emu oil and her hair has been restored.

7 Prior to this patient's ingestion of emu oil, testing on Jul. 27, 1993 yielded the following results:

Total cholesterol	292 mg/dl
HDL	40 mg/dl
Chol./HDL	7.3
LDL	205 mg/dl
Triglycerides	233 mg/dl

8 Subsequent to ingestion of emu oil of approximately one teaspoon per day, testing on Feb. 2, 1994 yielded the following results:

Total cholesterol	264 mg/dl
HDL	38 mg/dl
Chol./HDL	7
LDL	179 mg/dl
Triglycerides	239 mg/dl

9 EXAMPLE 3

10 For the prevention and treatment of allergies, a mature human female aged 60 years, has, for a time period of between six months and one year, coated the inside of her nostrils with the emu oil. As a result, the seasonal allergies she usually suffers have been alleviated.

11 Examples 4 and 5 illustrate the use of emu oil for preventing scarring.

12 EXAMPLE 4

13 A mature human male suffered a deep elongated cut and applied the emu oil to the cut, the expected scar did not result.

14 EXAMPLE 5

15 An immature human male aged 13 years impaled his finger on a fish hook. Upon removal of the fish hook emu oil was applied and the expected scar did not result.

16 Example 6 illustrates the use of emu oil for alleviating headaches. When using emu oil for treating a headache, the emu oil should be applied to the forehead and temples.

17 EXAMPLE 6

18 A mature human female having a severe migraine headache applied emu oil to her temples. As a result of applying the emu oil, the patient's migraine was alleviated. Normally, this patient would have to go to her doctor to receive a shot to alleviate her migraine.

19 Example 7 illustrates the use of emu oil for preventing nose bleeds, especially chronic nosebleeds. Emu oil can be used to prevent nose bleeds by application of a coating of emu oil inside the nostrils.

20 EXAMPLE 7

21 Emu oil was applied to the inside of the nostrils of an immature human male who normally has chronic nose bleeds. As a result of using the emu oil, on a daily basis, the usual nose bleeds did not occur.

22 Examples 8 and 9 illustrate the use of emu oil for preventing and treating cold and flu symptoms.

23 EXAMPLE 8

24 A mature human female, aged 60, who normally suffers from bad colds and the flu on a constant basis and who was always on antibiotics, applied emu oil on a regular basis inside her nostrils and ingested approximately one teaspoon per day of emu oil and was able to substantially prevent contraction of a cold or flu. Additionally, when the patient did suffer from congestion, additional application inside her nostrils alleviated her congestion. Further, when the patient did suffer a sore throat, application of emu oil on the back of her tongue alleviated her sore throat.

25 EXAMPLE 9

26 On Aug. 23 and 24, 1994 a mature human female, aged 27 years, was able to relieve her sore throat by placing approximately one quarter of a teaspoon of emu oil on her tongue, near the back of her tongue. On Aug. 25, 1994 this patient no longer had a sore throat.

27 Example 10 illustrates the effectiveness of emu oil for treating premenstrual syndrome (PMS).

28 EXAMPLE 10

29 A mature human female aged 38 ingesting emu oil on a regular basis of approximately one teaspoon per day no longer suffers from PMS and is relieved of suffering during her menstrual period. The patient also has a shortened menstrual period. The patient's usual symptoms of PMS and ailments during her menstrual period include stomach cramps, backaches, headaches and painful swelling, all of which the patient no longer suffers.

30 Emu oil can be used as a chemical buffer. Application of glycolic acid in skin treatments normally causes redness and irritation. The present inventors combined glycolic acid with emu oil, which operated as a buffer, such that the normal redness and irritation experienced upon application of glycolic acid were absent. Example 11 is illustrative of the use of emu oil as a chemical buffer.

31 EXAMPLE 11

32 Combined 7% emu oil with 10% glycolic acid in a 2 oz. jar.

33 Use of the preparation of Example 11 did not cause redness and irritation. Normally, it is not possible to use a preparation containing 10% glycolic acid due to the high level of irritation which results. However, in Example 11, emu oil acts as a chemical buffer to enable use of a preparation containing glycolic acid.

34 The present invention includes any known means of administration for administering emu oil. Generally known topical, systemic, enteral, rectal, parenteral and oral means of administration for administering emu oil are included in the present invention. Included as modes of administration are ingestion of emu oil by spoon, dropper or gelatin capsule, including time release capsules, directly into the patient's mouth or added to the patient's food. In accordance with the present invention, the patient may ingest an emulsion of emu oil. Accordingly, oral administration of emu oil may be in the form of tablets, capsules, emulsions, suspension, powders, etc., without limitation. Additionally, topical applications of the emu oil are beneficial for preventing and treating scars, preventing and treating headaches (especially migraine headaches), preventing and treating allergies and preventing and treating nose bleeds. Systemic administration may include subcutaneous or intramuscular injections of emu oil alone or in conjunction with a neutral vehicle. For parenteral administration, sterile solutions or emulsions are preferred.

35 The inventors do not know exactly how emu oil operates to achieve the benefits described above. However, it is hypothesized the effectiveness of emu oil in the Examples outlined above results from it being readily absorbed by the body and operating at a cellular level.

36 Having described the invention it will be appreciated that the present invention is not limited to that described above and that various changes and modifications can be effected therein by one of ordinary skill in the art without departing from the scope or spirit of the invention as defined by the appended claims.

CLAIMS:

What is claimed is:

1. A method of decreasing low density lipoproteins comprising administering to a patient an amount of emu oil effective for decreasing low density lipoproteins, wherein the mode of administration is selected from the group consisting of oral, enteral, rectal, parenteral and systemic.

2. The method of claim 1, wherein the effective amount of emu oil is 2-10 milliliters.

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L3: Entry 1 of 8 File: USPT Feb 14, 1995

US-PAT-NO: 5389373
DOCUMENT-IDENTIFIER: US 5389373 A

TITLE: Preparation of oil-in-water emulsions of drugs

DATE-ISSUED: February 14, 1995

INVENTOR-INFORMATION:

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PARENT-CASE:
This is a continuation of application Ser. No. 07/834,292, filed Feb. 24, 1992, now abandoned.

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US-CL-CURRENT: 424/400; 514/31, 514/938

FIELD-OF-SEARCH: 424/400, 514/938, 514/31

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4684633	August 1987	Imagawa et al.	514/938
☐	4707470	November 1987	Kirsh et al.	514/938
☐	4784845	November 1988	Desai et al.	514/938
☐	4816247	March 1989	Desai et al.	514/938
☐	4831018	May 1989	Kirsh et al.	514/938
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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
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0202837	November 1986	EP	
0296845	December 1988	EP	
0317120	May 1989	EP	

ART-UNIT: 152

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ABSTRACT:

A process for preparing an oil-in-water emulsion of a drug which is poorly soluble in water wherein the drug (e.g. amphotericin B) is dissolved in a solution of high or low pH prior to the formation of the drug emulsion. The solution of high pH is preferably a 0.5M solution of sodium hydroxide and/or potassium hydroxide and the solution of low pH is preferably a 0.5M solution of hydrochloric acid. The process comprises the steps of (a) dissolving the drug in a solution of high or low pH, (b) adding the resulting solution to a pre-formed emulsion, (c) adding to the emulsion an amount of an acid, base or buffer appropriate to neutralise at least substantially the product of step (b), and (d) where an acid or base is added in step (c), optionally adding sufficient buffer to adjust the pH of the product of step (c) to a desired value. A drug emulsion made by the process is also provided, in which the drug is primarily associated with the oil droplets.

17 Claims, 3 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

BRIEF SUMMARY:

1 The antibiotic amphotericin B is extremely beneficial in certain infectious conditions, particularly those caused by the fungal organism Candida. A common therapy is in the form of a product called Fungizone (Regd. T. M., Squibb) which consists of a solubilised formulation of amphotericin in the natural surfactant material sodium deoxycholate. This product is marketed by the Squibb Company. While helpful in combating Candida infections this product is not without its adverse reactions and side effects. It has been shown clearly that the Fungizone formulation can have a toxic effect particularly towards the kidney (see for example Reynolds et al (1963), Med. Clin. North American 47 1149-1154). The

antibiotic properties of amphotericin are due to its binding to sterols in cell membranes and the subsequent formation of a membrane pore. The binding to ergosterol, the primary fungal sterol, is stronger than the binding to the mammalian sterol cholesterol. Hence the toxicity of amphotericin is only selective for fungal cells and not specific; this is the origin of the side effects in patients. Alternative strategies for administering amphotericin have been investigated and work conducted in Texas by Juliano, Lopez-Berenstein and others is particularly noteworthy (see for example Mehta et al (1984), Biochem. Biophys. Acta 770 230-234). These workers have employed a liposome formulation (phospholipid vesicle) in order to achieve benefit in terms of therapy. Others working along similar lines include the Squibb Company itself with the pro-liposome concept (see for example Payne et al (1987), J. Pharm, Pharmacol. 39 24-28). While the liposomal system might be beneficial clinically it is well known that liposomes are normally difficult to prepare reproducibly in bulk and can be unstable.

2 While it is possible to produce an amphotericin emulsion system by the simple admixture of a commercial fat emulsion product (Intralipid, (Regd. T. M., Kabi) with the commercial solubilised system of amphotericin (Fungizone) (see, for example, EP-A-202 837), this system is unstable in that it produces a precipitate of the drug after this admixture and also has poor stability if stored for more than a few hours. The amphotericin B apparently is not intercalated at the oil-water interface in the additive formulations.

3 EP-A-215 313 (American Cyanamid) discloses certain emulsions which break easily on administration to a patient. The drug is mixed with an oil phase before water is added to form an emulsion. Benzyl alcohol is used as a co-surfactant. The emulsions not only break quickly on administration but are not very stable in storage.

4 WO 82/01821 (Chinoin) discloses formulations which have the drug as a solid suspension dispersed throughout an emulsion. Again, the emulsions are not very stable and do not overcome the problem of toxicity of the drug; it is to be noted that all the prior formulations are for topical application.

5 EP-A-211258 (Abbott) discloses certain micro-emulsions, which are quite distinct from the emulsions of the present invention.

6 Our earlier application EP-A-296 845 describes the preparation of an oil-in water surfactant-stabilised drug emulsion in which the drug is present in the surfactant layer. This was found to reduce the problems of toxicity and stability encountered with prior formulations. However, the drug emulsion has to be sterilised, for example by heat treatment, and this may result in loss of around 10% of the drug. The resulting product is perfectly usable but it would clearly lead to cost savings if such losses could be avoided.

7 It is the intention of the present invention to provide a process for preparing a drug emulsion which reduces loss of activity of the drug during formulation.

8 The invention provides a process for preparing an oil-in-water emulsion of a drug which is poorly soluble in water wherein the drug is dissolved in a solution of high or low pH prior to the formation of the drug emulsion. A "solution of high pH" is a solution with a pH of at least 9, preferably at least pH 11. A "solution of low pH" is a solution with a pH of 5 or less, preferably pH3 or less.

9 Advantageously, the solution of high pH is a solution of sodium hydroxide, which is preferably between 0.1M and 5.0M, .more preferably 0.5M. Potassium hydroxide may also be used, or a mixture of sodium and potassium hydroxide, to the same strength. A mixture of sodium and potassium may be advantageous to avoid disturbing the body's sodium/potassium ion balance. Any combination of sodium or potassium hydroxide may be used, and the proportions of these may be varied if this would be of clinical benefit to the individual patient.

10 Conveniently, the solution of low pH is hydrochloric acid, preferably at a

concentration of between 0.1M and 5.0M, more preferably about 0.5M. Any clinically acceptable acid may be used providing that it induces a large enough change in solubility of the drug. This can be readily determined by a person skilled in the art.

11 Preferably, the process comprises the steps of (a) dissolving the drug in a solution of high or low pH, (b) adding the resulting solution to a pre-formed emulsion, (c) adding to the emulsion an amount of an acid, base or buffer appropriate to neutralise at Least substantially the product of step (b), and (d) when an acid or base is added in step (c), optionally adding sufficient buffer to adjust the pH of the product of step (c) to a desired value. After addition of acid or base in step (c), a small sample of the emulsion may be withdrawn and tested by any suitable means to see if the pH is at the desired value. If it is not, buffer can be added. It will usually be desirable to have a neutral emulsion, i.e. about pH 7.4.

12 Any acid, base or buffer which is clinically acceptable may be used in step (c). Desirably, the acid is hydrochloric acid, acetic acid or glucuronic acid, the base is sodium hydroxide or potassium hydroxide and the buffer is an amino acid buffer or a phosphate buffer.

13 Any commercially available, parenterally acceptable emulsion may be used, for example Intralipid (Regd. T. M.), Ivelip (Regd. T. M.), Lipofundin (Regd. T. M.), Elolipid (Regd. T. M.), Endolipid and the MCT/LCT emulsion available from Braun. A typical emulsion may contain 3% to 30% soya, safflower or coconut oil (although coconut oil would not be used i.v.) and 0.2% to 5% of a parenterally acceptable emulsifier such as egg or soya lecithins, which may have been fractionated or hydrogenated to provide specific properties. The emulsion may also contain a tonicity adjusting agent such as glycerol, and amino-acids and glucose. The formulation and properties of such systems are familiar to those skilled in the art.

14 The procedure may also be used to add a hydrophobic drug to any parenterally acceptable dispersion for which the drug has sufficient affinity, such as liposomes, microparticulates or microemulsions.

15 A salt will be formed by the acid and alkali in the emulsion. In the case of sodium hydroxide and hydrochloric acid, sodium chloride will be formed; to avoid destabilisation of the emulsion, the final concentration of the salt should be less than 50 mM, preferably less than 10 mM. The presence of this salt will contribute to the tonicity of the drug emulsion. It may therefore be possible to use a pre-formed emulsion which contains little or no tonicity agent.

16 Desirably, the solution resulting from step (a), the pre-formed emulsion, the acid and the buffer, if used, are sterile at the time of use in the process described above. This can be achieved by carrying out the additions of solutions in steps (b), (c) and (d) by injection through a sterility filter. Such filters are well known to those skilled in the art. The pore size of the filter should be sufficiently small to remove all microorganisms, thus rendering them sterile. A 0.2 .mu.m pore would be suitable. No other sterilisation step, such as heat treatment, is required, although pyrogen-free materials should be used to avoid toxic shock. This has been found to reduce the problem of loss of drug activity usually encountered by such sterilisation procedures.

17 A second aspect of the invention provides an emulsion formed by the process described above in which the drug is primarily associated with the oil droplets. By "primarily associated with", we mean that at least 50% of the drug is associated with the oil droplets, preferably 60%, 70%, 80%, 90% or 99%. Most preferably, substantially all of the drug is associated with the oil droplets. The oil droplets may be separated from the emulsion by centrifugation and the drug shown to be in the oil layer.

18 The drug used in the emulsion is preferably one which is poorly soluble in water. By poorly soluble, we mean one which is insufficiently soluble for therapeutic levels to be achieved by the administration of a convenient volume

of a solution of the drug, In terms of an infusion of a formulation containing the drug, it would generally be the case that one would wish to administer less than 100 ml of the formulation per hour, preferably less than 50 ml/hour, more preferably less than 30 or 10 ml/hour. In essence, the formulations of the invention are particularly suitable for drugs which would be categorised in pharmacopoeias as "practically insoluble" in water. However, the drug must be soluble at either low or high pH.

19 The person skilled in the art will readily be able to determine by routine and non-inventive experiments whether a drug is suitable.

20 The drug may be a general anaesthetic, local anaesthetic, hypnotic, sedative, autacoid or autacoid antagonist (for example a prostaglandin), antibiotic or antimicrobial, antineoplastic (especially cytotoxic drugs such as methotrexate) or immunosuppressant. A particularly preferred group of drugs is the polyene antibiotics including tetraenes such as nystatin, pentaenes such as aliomycin, methylpentaenes such as filipin, carbonylpentaenes such as mycoticin, hexaenes such as cryptocidine, carbonylhexaenes such as dermostatin, and heptaenes such as amphotericin B. Such antibiotics are commercially available or can be conventionally prepared by techniques known to one of skill in the art. Preferably, the said drug is amphotericin B, nystatin or filipin, most preferably amphotericin B. For these drugs, strong alkali is used in the first step of the process. Strong acid may be used to dissolve basic drugs such as amodiaquine, bupivacaine, chlorcyclizine, chlorpromazine, dextromethorphan, diphenhydramine, ethopropazine, fenfluramine, fluopromazine, fluphenazine, imipramine, meclozine, nortryptyline, phenazocine, phencyclidine, promazine, promethazine, trifluoroperazine, triflupromazine or verapamil, or other active compounds which form soluble acid salts, especially hydrochlorides.

21 The level of drug may be chosen by one skilled in the art to suit the dosage regimen and so on but may typically be up to 5 mg/ml, preferably about 1 or 2 mg/ml, in the case of amphotericin B.

22 Emulsions in accordance with the invention can be administered topically, orally, rectally or by "aerosolisation" into the lungs, but will usually be administered parenterally, for example by continuous intravenous infusion or by injection, which may be intravenous, subcutaneous or intramuscular. Sustained release preparations such as subcutaneous depots may be used. The daily dose will be determined by the skilled person, with reference to the patient, the disease and the drug, but might typically be 0.10 mg/kg/day to 10 mg/kg/day, total body weight.

23 In the case of the polyene antifungal drugs such as amphotericin B, the formulations of the invention are useful in the treatment of humans or animals suffering from a variety of fungal infections, for example caused by any species of Candida (especially C. albicans and C. tropicalis), Torulopsis glabrata and Aspergillus spp. These infections are especially common, and serious, in immunocompromised patients, such as those treated with immunosuppressant drugs or those suffering from Acquired Immunodeficiency Syndrome (AIDS; acute HIV infection).

24 The emulsion of the present invention may be made up by a manufacturer, or by a pharmacist immediately prior to use. The latter situation may be advantageous for drugs which destabilize the emulsion. The drug emulsion would then have to be made immediately prior to use. An alternative embodiment of the invention therefore provides a kit comprising (a) a known amount of drug (b) a known amount of solution of high or low pH, and (c) an amount of acid, base or buffer appropriate to at least substantially neutralise the solution of high or low pH. Conveniently, the kit additionally comprises (i) a preformed emulsion, and (ii) at least one sterility filter.

25 The drug emulsion may be used as part of a total parenteral nutrition (TPN) system. In this case, the drug emulsion is formulated and is then compounded with the TPN constituents, (sugars, amino acids, etc). This avoids destabilization of the TPN mixture. For some drugs, where the volume of solution

used in step (a) of the formulation process is small, it may be possible to omit the neutralisation step (c) as the TPN mixture may itself have sufficient buffering capacity to neutralise the emulsion.

26 The process of the present invention is simple to carry out and has been found to produce an emulsion which has increased particle size stability. The process also avoids the use of a co-solvent for the drug, such as methanol. The presence of such a solvent in an emulsion for parenteral administration is regarded by many as unacceptable, even when present only in traces.

27 A preferred embodiment will now be described by way of example and with reference to the accompanying drawings in which FIG. 1 shows a conventional bacterial filter and FIGS. 2 and 3 show toxicity data.

DETAILED DESCRIPTION:

1 EXAMPLE 1

2 Preparation of an Amphotericin B emulsion

3 100 mg Amphotericin B was dissolved in 2 ml of 0.5M sodium hydroxide with the aid of sonication. The solution was then drawn into a syringe and injected through a 0.2 .mu.m filter as shown in FIG. 1 into a 100 ml bottle of Intralipid 20%. 2 ml of water for injection was then drawn into the syringe and injected into the emulsion through the same filter. 2 ml of 0.5M hydrochloric acid was then injected into the emulsion through the filter and followed by 2 ml of water for injection. 2 ml of 0.1M phosphate buffer at pH 7 was then added. The whole bottle was thoroughly mixed by shaking.

4 The filter of FIG. 1 comprises a sealed housing 1 having respective top (entry) and bottom (exit) ports 2,3 for liquids, the housing 1 being divided into two compartments 4,5 by a 2 .mu.m pore membrane filter 6 supported on a filter support 7. Liquid to be sterilised enters the first compartment 4, passes through the filter 6 into the second compartment 5 and, thus sterilised, leaves through the exit port 3.

5 EXAMPLE 2

6 Stability of the emulsion

7 The emulsion prepared by the above method showed no detectable increase in droplet size over a 50 day period. (Malvern Mastersizer; D (v. 0.9)=0.72 .mu.m at t=0, 0.68 .mu.m at t=50 day).

8 EXAMPLE 3

9 Stability of the Amphotericin B

10 The emulsion was dispersed in dimethyl sulphoxide and the absorbance of amphotericin was measured at 514 nm.

11 The amphotericin B concentration decreased from 0.46 mg/ml at t=0 to 0.43 mg/ml after 50 days.

12 EXAMPLE 4

13 Toxicity of Amphotericin B emulsion to canine kidney cells in monolayer culture

14 The toxicity of a formulation prepared as in Example 1 above to canine kidney cells was measured in monolayer culture for extended periods. The cell line (MDCK NBL-2) was established in a modified MEM medium and grown as a confluent monolayer on Millicell HA filters. The integrity of the monolayer was measured via its resistance. The cell monolayers were transferred to calcium- and

magnesium-free Hanks' balanced salt solution (HBSS) to avoid emulsion flocculation, concentrations of amphotericin B formulations up to 100 .mu.g/ml were added, and the resistance measured over a period of 48 hours. Control experiments were performed with an amphotericin-free emulsion (Intralipid 20% and a commercial amphotericin formulation (Fungizone, Squibb). A typical plot of resistance vs. time is shown in FIG. 2 (amphotericin concentration 10 .mu.g ml.sup.-1). Fungizone is represented by solid squares, Amphotericin emulsion by open squares and the Intralipid control by open circles. The loss of confluence on addition of Fungizone is evident within 6 hours, and is demonstrated by a severe drop in monolayer resistance. Only a small decrease is observed using either the Intralipid control or the amphotericin emulsion formulation, and we believe this to be due to minor changes in cell viability after changing to low-salt HBSS medium. The dose-response curve, calculated as a percentage of the control resistance after 6 hours, is shown in FIG. 3. Fungizone is represented by solid squares and the Amphotericin emulsion by open squares. The low toxicity of the emulsion formulation is maintained up to an amphotericin concentration of 100 .mu.g ml.sup.-1.

15 The results clearly demonstrate the low toxicity to kidney cells of the amphotericin B emulsion formulation.

16 EXAMPLE 5

17 Preparation of chlorpromazine emulsion

18 To make approximately 100 ml of an emulsion containing 2 mg/ml chlorpromazine.

19 Chlorpromazine (200 mg) was dissolved in hydrochloric acid (0.5M; 2 ml) and injected through a 0.2 .mu.m filter into a 100 ml bottle of Intralipid 20%. The filter was rinsed through with 2.times.1 ml portions of water for injection. Sodium hydroxide (0.5M, 2 ml) was then injected through the same filter, followed by phosphate buffer (0.5M, pH 7.0, 1 ml). The bottle was swirled continuously during all additions.

CLAIMS:

We claim:

1. A process for preparing an oil-in-water emulsion of a drug which is poorly soluble in water, said process comprising the steps of:

(a) dissolving the drug in a solution of high pH having a pH of at least 9 or low pH having a pH of 5 or less;

(b) adding the resultant solution to a pre-formed emulsion;

(c) adding to the emulsion an amount of an acid, base or buffer appropriate to neutralize at least substantially the product of step (b).

2. A process according to claim 1, wherein said solution of high pH is selected from the group consisting of a solution of sodium hydroxide and potassium hydroxide between 0.1M and 5.0M.

3. A process according to claim 2, wherein the hydroxide solution is substantially 0.5M.

4. A process according to claim 1, where the drug is a polyene antibiotic.

5. A process according to claim 4, wherein the drug is amphotericin B.

6. A process according to claim 1, wherein the solution is a solution of low pH and is hydrochloric acid between 0.1M and 5.0M.

7. A process according to claim 6, wherein the hydrochloric acid is substantially 0.5M.

8. A process according to claim 1, wherein, when an acid or base is added in step (c), sufficient buffer is added to adjust the pH of the product of step (c) to a desired value.

9. A process according to claim 8, wherein the acid used in step (c) is selected from the group consisting of hydrochloric acid, acetic acid and glucuronic acid, the base used in step (c) is selected from the group consisting of sodium hydroxide and potassium hydroxide and the buffer used in step (c) is selected from the group consisting of an amino acid buffer and a phosphate buffer.

10. A process according to claim 8, wherein the final concentration of salt formed in the emulsion is less than 50 mM.

11. A process according to claim 10, wherein the final concentration of salt formed in the emulsion is less than 10 mM.

12. A process according to claim 1, wherein the solution resulting from the step (a), the preformed emulsion, and the acid, base or buffer of step (c) are sterile at the time of use in said process.

13. A process according to claim 8, wherein the solution resulting from the step (a), the preformed emulsion, and the acid or base of step (c) and the buffer added to adjust the pH of the product of step (c) to a desired value are sterile at the time of use in said process.

14. An emulsion made by the process according to claim 1, wherein the drug is poorly soluble in water and is primarily associated with the oil droplets.

15. A kit for making an oil-in-water emulsion of a drug which is poorly soluble in water, comprising:

(a) known amount of said drug which is poorly soluble in water;

(b) a known amount of a solution of high pH having a pH of at least 9 or low pH having a pH of 5 or less; and

(c) an amount of acid, base or buffer appropriate to neutralize at least substantially the solution of high or low pH.

16. A kit according to claim 15, additionally comprising (i) a pre-formed emulsion and (ii) at least one sterility filter.

17. A method of treating or preventing disease in a human or other animal, said method comprising the step of administering to the human or animal an effective non-toxic amount of an emulsion of a drug which is poorly soluble in water made according to the process of claim 1.